



October 18, 2004

United States
Department of
Agriculture

Animal and Plant
Health Inspection
Service

Washington, DC
20250

VETERINARY SERVICES MEMORANDUM NO. 800.110

Subject: Exemption from Label Warning Concerning the Use of Bovine Rhinotracheitis Vaccine, Modified Live Virus in Pregnant Cows or in Calves Nursing Pregnant Cows Under 9 Code of Federal Regulations 112.7(e)

To: Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics

I. PURPOSE

This memorandum provides guidance for claiming an exemption to the requirement for a label statement warning against the use of Bovine Rhinotracheitis Vaccine, Modified Live Virus in pregnant cows or in calves nursing pregnant cows.

II. BACKGROUND

Title 9, *Code of Federal Regulations* (9 CFR), section 112.7(e) requires Bovine Rhinotracheitis Vaccine containing modified live virus to bear the following statement: "Do not use in pregnant cows or in calves nursing pregnant cows." The Administrator, Animal and Plant Health Inspection Service may grant an exemption to this requirement under 9 CFR 113.4 (a), provided, that such vaccine has been shown to be safe for such use. This memorandum provides guidance concerning the type of data needed to obtain the exemption.

Although a label statement is not required under the regulations at this time, Bovine Virus Diarrhea Vaccine containing modified live virus also is not recommended for use in pregnant cows or in calves nursing pregnant cows. The guidance concerning the type of data needed to obtain an exemption for Bovine Rhinotracheitis Vaccine, Modified Live Virus may also be used to support a label claim for use in pregnant cows or in calves nursing pregnant cows for Bovine Virus Diarrhea Vaccine containing modified live virus. Bovine Virus Diarrhea Vaccine, Modified Live Virus, containing noncytopathic bovine viral diarrhea virus (BVDV) may not be recommended for use in pregnant cows or calves nursing pregnant cows.

To obtain an exemption to the warning statement required under 9 CFR 112.7(e) for Bovine Rhinotracheitis Vaccine containing modified live virus, and to support a label statement for use in pregnant cows and calves nursing pregnant cows for Bovine Virus



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Diarrhea Vaccine containing modified live virus, the supporting study should be designed in accordance with the following parameters.

III. GUIDELINES

Only heifers and cows that are confirmed pregnant should be included in the study. All animals should be vaccinated with an appropriate single or multifraction test vaccine. Animals must be vaccinated in accordance with product labeling including, if recommended, a pre-breeding vaccination. If vaccination prior to breeding is not required, all animals must be seronegative for virus prior to administration of the test vaccine. Studies that only involve the vaccination of calves that are nursing pregnant heifers or cows will not be acceptable for claiming the exemption. Clinical studies should be conducted in accordance with Veterinary Services Memorandum 800.301, Good Clinical Practice.

A. Perform a Controlled Study

1. *Animals* - At least 1,200 pregnant heifers and cows must be included in the study. Animals should be divided into three groups of 400 animals each on the basis of stage of pregnancy, i.e., first, second, or third trimester.
 - a. Three separate studies may be conducted; however, at least 400 animals are needed for each stage of pregnancy.
 - b. All animals included in the study must be followed through parturition.
2. *Randomization* – Randomly divide each group (trimester) into two groups (vaccine and controls) each containing 200 animals.
 - a. Inoculate animals in the vaccine group with the modified live virus test vaccine.
 - b. Inoculate animals in the control group with inactivated vaccine or phosphate buffered saline.
 - c. The groups should be adequately separated so as to prevent the controls from being exposed to vaccines that may be shedding vaccine virus.

B. Vaccine

Vaccine used in the study should be formulated in accordance with the filed Outline of Production. If vaccination prior to breeding is recommended, the identity of the vaccine used for the pre-breeding vaccination should be specified in the report and on the labeling.

C. Data

For each group, the calving rate, the health status of the calves up to 4 weeks post partum, and the Clopper-Pearson 95% confidence interval for the aborting fraction should be determined and summarized in the study report.

1. *Abortions* – Animals that do not deliver a live calf will be counted as abortions, cause unknown. Abortions due to diagnosed causes other than BVDV or infectious bovine rhinotracheitis virus (IBRV) will be excluded from the data analysis.

a. Aborted calves should be necropsied and the results included in the study report.

b. The study must be repeated for any trimester group in which the rate of abortion due to any cause exceeds 5%.

c. An exemption may not be approved if the rate of abortion due to IBRV or BVDV exceeds 0.5% in any trimester group.

2. *Bovine viral diarrhea virus* – To detect BVDV capable of causing fetal infection without causing abortion, pre-suckling serum samples from at least 100 randomly chosen calves from the second and third trimester pregnancy groups (50/group) should be tested for antibody to types 1 and 2 BVDV, and IBRV; an exemption may not be approved if any animal has a positive test.

3. *Adverse events monitoring* – The Center for Veterinary Biologics (CVB) may monitor adverse events reported to the company and compare the number of adverse event reports per number of doses of vaccine marketed received by the firm after the exemption to the number of adverse event reports per number of doses of vaccine marketed received by the firm prior to the exemption. If evidence of safety problems is encountered, CVB will take appropriate actions.

D. Labeling

Labeling (including insert) should include a statement indicating that the vaccine may be used in pregnant cows, and calves nursing pregnant cows, with a brief description of the study, and summary of the results.

1. *Pre-breeding Vaccination* – If vaccination prior to breeding is required, the recommended product and dose should be specified on the label. Multifraction vaccine(s) produced by the same manufacturer also may be recommended: provided, that they are produced using the same master seed virus, master cell stock, and serial release titer as the test vaccine. Suggested wording acceptable to CVB is: “This vaccine may be used in pregnant cows or calves nursing pregnant cows provided they were vaccinated pre-breeding with (insert the name of the product).”

2. *Label Warning* – Labeling may include any factual statement communicating the risks associated with vaccinating pregnant animals using modified live virus vaccine; including a recommendation to discuss the implications with a veterinarian. The suggested wording acceptable to CVB is: Warning: “Fetal health risks associated with vaccination of pregnant animals with modified live vaccines cannot be unequivocally determined by clinical trials conducted for licensure. Management strategies based on vaccination of pregnant animals with modified live vaccines should be discussed with a veterinarian.”

3. *Aborting Fractions* – Because the treatment groups may not have been commingled during the study, inferences concerning any relationship between the calculated aborting fraction(s) for the groups must be reviewed by CVB.

IV. ACTION

Protocols should be submitted to CVB for review prior to the initiation of any study. Upon the successful completion of a study and acceptance of the data, CVB will approve an exemption to the labeling requirement under 9 CFR 112.7 (e).



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